REMARKS

In the Action, claims 1-10 are rejected. In response, claims 1 and 3-8 are amended, new claims 11 and 12 are added, and claims 2, 9 and 10 are cancelled.

Independent claim 1 is amended to recite a method of treating neurodegenerative disease by administering an effective amount of the compound of Formula I. Claim 1 is also amended to define the R groups are in original claims 2 and 3. In particular, R_1, R_2, R_3 and R_4 are amended to recite a hydrogen or an alkyl having 1 to 6 carbon atoms as in original claim 2. Claim 1 is also amended to recite that N is an integer from 6 to 10 as in original claim 3. The dependent claims are amended to be consistent with the amendments to claim 1. New claims 11 and 12 are added to depend from claims 1 and 8, respectively. Claim 11 is directed to the method of administering the specific compounds to treat the symptoms of Parkinson's disease or ischemia/reperfusion injury. Claim 12 is amended to recite the specific dosage of the compound. These claims are supported by the specification as originally filed.

In view of these amendments and the following comments, reconsideration and allowance are requested.

Rejections Under 35 U.S.C. § 112

The claims are rejected under 35 U.S.C. § 112, first paragraph and second paragraph. The claims are amended to overcome the rejections under 35 U.S.C. § 112, second paragraph, as outlined in paragraphs 6-8 of the Office Action.

Applicants submit that the invention as recited in the claims is enabled by the specification in accordance with 35 U.S.C. § 112, first paragraph. The claims are directed to a

method of treating a neurodegenerative disease in an animal by administering an effective amount of the claimed compounds. Thus, the claims are not directed to treating any disease or pathology. The specification supports the claims as amended and provides an enabling disclosure for one skilled in the art to practice the invention.

In view of these amendments, the claims are submitted to be in proper form under 35 U.S.C. § 112, first paragraph and second paragraph.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-4 and 7-9 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,981,548 to Paolini et al. As amended, the claims are directed to a method of treating a neurodegenerative disease in an animal and are not directed to a method of producing the composition or to the composition *per se*. Thus, the claims are not anticipated by Paolini et al. Furthermore, the claims are amended to define the compound of Formula I in a manner that is not disclosed or suggested in Paolini et al. In view of these amendments, the claims are not anticipated by Paolini et al.

Rejection of Claim 10

Claim 10 is rejected under 35 U.S.C. § 103(a) as being obvious over Paolini et al. Claim 10 is cancelled to obviate this rejection.

Rejection of Claims 5 and 6

Claims 5 and 6 are rejected under 35 U.S.C. § 103(a) as being obvious over Paolini et al., and further in view of EP 1132085 to Ito et al., U.S. Patent No. 5,036,097 to Floyd et al., and U.S. Patent No. 6,420,429 to Atlas et al. Paolini et al. is cited for disclosing the claimed compounds suitable for use as a superoxide scavenger. Ito et al. is cited for disclosing that oxygen free radicals cause various *in vivo* reactions including ischemic disease and nervous disease accompanied by nerve degeneration. Floyd et al. is cited for disclosing that certain oxygen scavengers are therapeutically effective for treating ischemia. Atlas et al. is cited for disclosing that oxygen scavengers are generally effective for the treatment of Parkinson's disease.

Applicants respectfully submit that the claims are not obvious to one skilled in the art over the combination of the cited patents. Paolini et al. relates to antioxidant compounds and compositions. Paolini et al. does not disclose or suggest a method of treating a neurodegenerative disease using the compounds as defined in amended claim 1. Ito et al., Floyd et al. and Atlas et al. disclose generally antioxidants for various uses. In view of the combination of the cited patents, one skilled in the art would not be motivated to use the claimed compounds of amended claim 1 to treat neurodegenerative diseases as in the claimed invention. Moreover, Ito et al., Floyd et al., and Atlas et al. provide no reasonable expectation of success to one skilled in the art that the compounds of Paolini et al. would be effective in treating neurodegenerative diseases. Accordingly, the claims are not obvious over the combination of the cited patents.

The disclosure of Paolini et al. does not provide one of ordinary skill in the art with an expectation of success that the compounds of the claimed invention would be effective in the treatment of neurodegenerative diseases. Paolini et al. only discloses the ability of the

compounds to pass lypophilic barriers. The compounds of the claimed invention as disclosed in the specification are able to pass the blood-brain barrier to be effective in treating neurodegenerative diseases. The ability of the claimed compounds to pass the blood-brain barrier is unexpected and could not have been predicted based on the disclosure of Paolini et al. Furthermore, the ability of the claimed compounds to pass the blood-brain barrier is important in contributing to the efficacy of the claimed compounds in treating neurodegenerative diseases.

Example 1 in the present specification presents experimental data showing that the specific compounds MP1002 and MP1001 are able to cross the blood-brain barrier and that such compounds are able to protect the dopaminergic neurons of the *Substantia Nigra* against degenerative damage.

Paolini et al. discloses generally that the compounds are able to cross biological membranes, although this general disclosure does not enable one skilled in the art to reasonable predict that the same compounds would be able to cross the blood-brain barrier. Cellular membranes are constituted by a double phospholypid layer with hydrophobic heads which form the internal and external surfaces and hydrophobic tails which join together at the center of the membrane and other components such as carbohydrates, glycolipids, glycoproteins, cholesterol and proteins. The blood-brain barrier is a complex structure constituted by vascular endothelium and by a thick layer of astroglia cells (astrocytes). Furthermore, the blood-brain barrier is formed by a network of closely sealed endothelial cells in the brain capillaries which expresses a high level of proteins that carry foreign molecules away from the brain while allowing others such as glucose and insulin that are necessary to the functioning of the brain cells to cross the barrier.

The make-up of the blood-brain barrier makes it difficult for molecules to cross such that the blood-brain barrier constitutes a true barrier for the molecules. It is known that only a small number of pharmaceutical molecules are capable of crossing the blood-brain barrier. Thus, it is clear that the disclosure of Paolini et al. suggests that the compounds are able to pass through the double lypoproteinic layer of the biological membranes as disclosed in column 2, lines 44-46, and does not refer to the blood-brain barrier. Paolini et al. provides no suggestion to one skilled in the art that the compounds are capable of passing through the blood-brain barrier.

To overcome the difficulties of formulating drugs which are able to pass through the blood-brain barrier to reach the central neurosystem, several strategies have been developed. These include chemical modifications of the molecules to increase their lyposolubility, the development of lyposome techniques, nanoparticles, pegylation, antisense drugs, direct injection such as infusion in the cerebrospinal fluid, intracarotideal infusion, the use of specific carriers, hypertonic solutions and the administration of lypophilic pro-drugs having a hydrophlicity that is lower than the drug to reinstate the active agent after crossing the blood-brain barrier by means of enzymatic hydrolysis. These proposals are rather complex, expensive and often times unsuccessful as demonstrated by the small number of commercial drugs that are capable of crossing the blood-brain barrier. For example, Vitamin E is a known lypophilic antioxidant which is able to cross the blood-brain barrier only in small amounts. In view of the rapid metabolism of Vitamin E, Vitamin E is not able to exert any pharmacological effect such that benefits from Vitamin E can only be obtained when the blood-brain barrier is damaged.

Vitamin C in its oxidated form (dehydroascorbic acid) is able to cross the blood-brain barrier. The commercial reduced forms of Vitamin C are not able to cross the blood-brain

barrier. Other natural anti-oxidants such as flavonoids and carotenoids are also not able to cross the blood-brain barrier.

In contrast, Applicants have found that the compounds recited in claim 1, namely, the aliphatic bis-hydroxylamine are able to easily cross the blood-brain barrier. This feature is demonstrated by Example 1 in the specification. The compounds of claim 1 as amended have a long aliphatic chain with 6 to 10 carbon atoms which increase the solubility in lipid phases. This requirement is fundamental and has an impact on the capacity of the molecules to form a limited number of hydrogen bonds which favor the affinity with apolar regions. At the same time, the molecule has a hydroxylamine group at the terminal end with a medium polarity so that it is partially soluble in the aqueous phase.

The claimed compounds provide a log P=4.01 which is between that of Vitamin E (log P=10.24) which is too highly lypophilic and that of ascorbic acid (log P=3.36) which is highly hydrophilic. The two aspects of the symmetric structure of the claimed molecules allow the molecules to distribute themselves at the level of the blood-brain barrier without remaining trapped as is the case with Vitamin E.

Based on the disclosure of Paolini et al., one skilled in the art would not be able to reasonable predict that the compounds as presently claimed would be able to pass the blood-brain barrier and thus be effective in treating neurodegenerative diseases. The secondary references do not provide the deficiencies of Paolini et al. As amended, the compounds recited in claim 1 are not similar to the compounds of Ito et al. Ito et al. does not suggest symmetric compounds as in the claimed invention. Furthermore, Ito et al. provides no teaching of the compounds as claimed which can be useful for the treatment of neurodegenerative diseases. In paragraph 0004 of Ito et al., various diseases are disclosed such as ischemic diseases, cranial nervous diseases accompanied by nerve degeneration

which are known as diseases accompanied by active oxygen and free radicals. This disclosure does not relate to the compounds disclosed in Ito et al. and refers only to a general indication of various diseases. Ito et al. discloses compounds that are generally used to treat diseases caused by active oxygen and free radicals *in vivo*, but provides no suggestion that the compounds are useful for the treatment of neurodegenerative diseases.

Paragraph 0059 of Ito et al. refers to compounds as a preventive therapeutic agent for diseases related to active oxygen. Paragraph 0056 of Ito et al. refers to the compounds for use as diagnostic agents for diagnosing diseases relative to active oxygen. These passages provide no suggestion of the therapeutical treatment of such diseases.

It is known that more than 130 human pathologies can be considered as related to an abnormal production of free radicals. It is not known if the free radicals are the cause or the effect of such pathologies. It follows that the fact that a compound has antioxidant and free radical scavenging properties does not necessarily mean that the same compound is useful for the treatment of a pathology associated with free radical production.

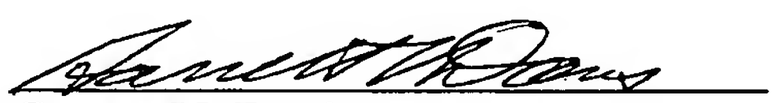
Atlas et al. also does not provide the deficiencies of Ito et al. and Paolini et al. Atlas et al. specifically discloses that all oxygen scavengers are not necessarily effective for the treatment of Parkinson's disease. The compound must be able to cross the blood-brain barrier. Furthermore, simply because the compound is able to cross the blood-brain barrier is not necessarily sufficient to treat Parkinson's disease. Thus, the passage in column 4, lines 40-44 of Atlas et al., does not support the position presented in the Action. The Examiner's attention is also directed to U.S. Patent No. 6,369,106 to Atlas et al. which is a continuation-in-part of Atlas et al. which discloses that treating ischemic brain injuries requires a compound having a combination of molecular weight and membrane miscibility properties to enable the compounds to cross the blood-brain barrier.

Floyd et al. also does not disclose the claimed compounds or that all oxygen scavengers are therapeutically effective. Accordingly, Floyd et al. does not suggest the claimed invention.

In view of the deficiencies of the cited patents, it would not have been obvious to one of ordinary skill in the art to administer the claimed compounds and a method of treating neurodegenerative diseases in an animal. One skilled in the art based on the disclosure of the cited patents would not have a reasonable expectation of success that the compounds would be able to pass the blood-brain barrier and would be effective in treating the claimed neurodegenerative disease. Accordingly, the claims are not obvious over the combination of the cited patents.

In view of these amendments and the above comments, reconsideration and allowance are requested.

Respectfully submitted,



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